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Enantioselective Cu-Catalyzed 1,4-Addition of Me_3Al to a 4,4-Disubstituted Cyclohexa-2,5-dienone: Novel Effect of TrialkylsilylOTf on Enantioselectivity

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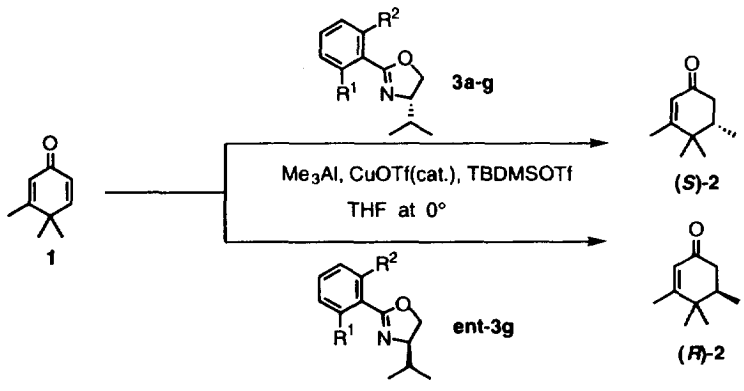
Abstract: The asymmetric Cu-catalyzed conjugate addition of Me_3Al to cyclohexa-2,5-dienone in the presence of 20 mol% of chiral 2-aryloxazolines and 120 mol% of TBDMSOTf gave the corresponding addition product in good yield with enantiomeric purities of up to 68% ee under mild conditions. Without TBDMSOTf, the ee was dramatically decreased, even in the presence of chiral 2-aryloxazolines.

Recently, considerable attention has been given to cyclohexa-2,5-dienones as versatile chiral synthons because of their multi-functionality.[1] Although several elegant methods have been developed to introduce chirality into achiral cyclohexa-2,5-dienones, most of these involve the temporary conversion of cyclohexa-2,5-dienones to chiral tricycloadducts by diastereoselective [4+2]-cycloaddition with chiral cyclopentadiene,[1a] and lipase-mediated or Rh(I)(chiral BINAP)-catalyzed asymmetrization of meso-tricycloadducts.[1b,c] To the best of our knowledge, only one example of direct chiral induction into achiral cyclohexa-2,5-dienone by Sharpless epoxidation has been reported (80% ee).[1d] This stimulated us to investigate other methods for differentiating the enantiotopic face of achiral cyclohexa-2,5-dienone using a carbon-carbon bond-forming reaction. Thus far, substantial progress has been achieved in both stoichiometric and catalytic asymmetric conjugate additions with chirally modified heterocuprates[2] or achiral cuprates in the presence of external chiral ligands,[3] and quite high enantioselectivities have been realized. However, there has been no reported examination of the asymmetric Cu-catalyzed conjugate addition of organometals to cyclohexa-2,5-dienones. Therefore, we investigated asymmetric Cu-catalyzed conjugate addition to 3,4,4-trimethylcyclohexa-2,5-dienone **1**[4] as a substrate under various asymmetric reaction conditions which had been successfully applied to enone-systems. However, only unsatisfactory results (low chemical yield and poor enantioselectivity) were obtained due to their poor reactivity. We finally found that the use of trialkylaluminium as the organometal[5] dramatically improved the chemical yield and gave an optically active 1,4-addition adduct (-)-**2** in up to 68% ee



3a: R^1=PhS, R^2=H
3b: R^1=Ph_2P, R^2=H
3c: R^1=R^2=H
3d: R^1=OMe, R^2=H
3e: R^1=O^{i}Pr, R^2=H
3f: R^1=^{n}Bu, R^2=H
3g: R^1=R^2=OMe

Scheme 1

in the presence of 20 mol% of (-)-(*S*)-2-(2,6-dimethoxyphenyl)oxazoline **3g** and 120 mol% of *tert*-butyldimethylsilyl triflate (TBDMSOTf) (Scheme 1). We describe here the effect of the aryl substituents (R^1 and R^2) of chiral oxazolines **3a-g** and the role of trialkylsilyl triflate on the enantioselectivity of asymmetric Cu-catalyzed conjugate addition to **1**.

We began our studies with the addition of trimethylaluminium (1.1 eq) to **1** in THF at room temperature in the presence of 1 mol% of copper bromide (CuBr) and 20 mol% of phenylthio-and diphenylphosphino-oxazolines **3a** and **3b**, which had been successfully used in enantioselective Pd-catalyzed allylic alkylations,[6] to give the 1,4-addition product (-)-**2** with poor enantioselectivity regardless of the presence of trimethylsilyl chloride (TMSCl) (entries 1-3). The addition of trimethylsilyl triflate (TMSOTf) instead of TMSCl had a beneficial effect on enantioselectivity and gave (-)-**2** in 14-48% ee, depending on the reaction temperature (entries 4-6). The enantioselectivity further increased to 63% ee when the reaction was carried out at 0 ℃ in the presence of TBDMSOTf, which is a more sterically hindered additive (entry 8). Changing the counter anions of the copper salts from bromide to triflate had no effect on enantioselectivity, but significantly affected the chemical yield (entry 9). Moreover, whereas an increased amount of Me_3Al (2 eq) improved both the chemical yield and ee of (-)-**2**, an increased amount of CuOTf (0.05 eq) improved only the chemical yield with a negligible loss of ee (entries 7 and 10). We next investigated other chiral 2-aryloxazoline analogues to identify a more efficient chiral ligand and to clarify the mechanism of chiral induction. Since no chiral induction was observed with 2-phenyloxazoline **3c**,[7a] the substituent on the aryl ring should play an important role in the asymmetric conjugate addition (entry 11). Considering that the alkoxy- and alkyl-substituted chiral ligands **3d-f**[7b] showed a similar ee in the conjugate addition, the substituents (R^1) may not participate in

Table 1. Asymmetric Conjugate Addition of Me_3Al to **1** with Chiral Oxazolines **3a-g** in the Presence of Several Additives

Entry	CuX	Ligand	Additive	Me_3Al/CuX/ ligand/Additive	Temp. ℃	Time hr	Yield[a] %	S/R[b]	Ee[b] %
1	CuBr	**3a**	none	1.1/0.01/0.2/0.0	rt	23	11	53/47	5
2		**3a**	TMSCl	1.1/0.01/0.2/1.2	rt	5	39	54/46	8
3		**3b**	TMSCl	1.1/0.01/0.2/1.2	rt	22	28	50/50	0.3
4		**3a**	TMSOTf	1.1/0.01/0.2/1.2	rt	2	37	69/31	37
5		**3a**	TMSOTf	1.1/0.01/0.2/1.2	0	5	28	74/26	48
6		**3a**	TMSOTf	1.1/0.01/0.2/1.2	-20	5	61	57/43	14
7		**3a**	TMSOTf	2.0/0.01/0.2/1.2	0	2	46	78/22	56
8		**3a**	TBDMSOTf	2.0/0.01/0.2/1.2	0	2	35	82/18	63
9	CuOTf[c]	**3a**	TBDMSOTf	2.0/0.01/0.2/1.2	0	2	53	82/18	63
10		**3a**	TBDMSOTf	2.0/0.05/0.2/1.2	0	2	66	80/20	59
11		**3c**	TBDMSOTf	2.0/0.05/0.2/1.2	0	1	61	50/50	0
12		**3d**	TBDMSOTf	2.0/0.05/0.2/1.2	0	0.5	88	73/27	45
13		**3e**	TBDMSOTf	2.0/0.05/0.2/1.2	0	0.5	70	80/20	59
14		**3f**	TBDMSOTf	2.0/0.05/0.2/1.2	0	2	48	73/27	46
15		**3g**	TBDMSOTf	2.0/0.05/0.2/1.2	0	1	88	84/16	68
16		**ent-3g**	TBDMSOTf	2.0/0.05/0.2/1.2	0	0.5	79	82/18	64

[a] Isolated yield. [b] Determined by HPLC analysis (DAICEL CHIRALPAK AS, hexane/2-propanol 7/3). [c] $Cu(I)\cdot 1/2C_6H_6$ complex was used.

coordination to the copper or aluminium atom, but may provide conformational restriction of the transition state via steric factors (entries 12-14). In addition, the alkoxy-substituted ligands **3d** and **3e** dramatically accelerated the reaction rate, giving (-)-**2** in good yields (70-88%). Expecting a more restricted transition assembly, we performed the reaction with a new chiral ligand, 2-(2,6-dimethoxyphenyl)oxazoline **3g**, which was prepared from commercially available 2,6-dimethoxybenzoyl chloride and (*S*)-valinol in two steps as previously reported,[8] to give (-)-**2** in 88% yield with a maximum ee of 68% (entry 15). Whereas (-)-(*S*)-**2**[9] was always obtained as a major product when (4*S*)- 4-isopropyl-2- aryloxazolines were used as a chiral ligand, the reaction with ent-**3g**[8] gave (+)-(*R*)-**2**[9] with a compatible ee value but a reverse sense (entry 16). This result strongly indicates that the induction of chirality in the asymmetric conjugate addition originates from the C4-chirality of the oxazoline ligands. The transition state model in Fig. 1 may explain the enantiofacial differentiation in the present asymmetric conjugate addition.[10] Dienone **1**, first activated by TBDMSOTf, approaches from the more accessible face (upper-right) of the MeCu-chiral ligand complex due to steric hindrance of the C4-isopropyl group and the C2-aryl ring of the ligand to form the TBDMS-activated dienone and copper π-complex. Interaction of the triflate anion with the copper atom makes the transition state more rigid. Therefore, (-)-(*S*)-**2** is the predominant product using both the (-)-(*S*)-chiral oxazoline ligand and trialkylsilyl triflate.

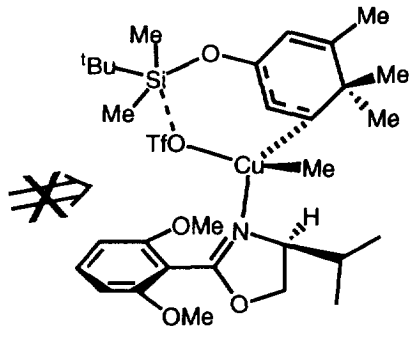


Fig. 1. Plausible transition state model for the reaction of **1** with a MeCu-**3g** complex

Typical procedure (Table 1, entry 15) is as follows: A solution of CuOTf•1/2C_6H_6 complex (1.9 mg, 7.5 mmol) and **3g** (7.5 mg, 0.030 mmol) in dry THF (2 ml) was stirred at room temperature for 30 min. After a solution of **1** (20.4 mg, 0.15 mmol) in THF (1 ml) had been added to the solution, 1.0 M solution of Me_3Al in hexane (0.30 ml, 0.30 mmol) and TBDMSOTf (0.04 ml, 0.18 mmol) were added successively to the reaction mixture at 0 ℃ and the whole was stirred at the same temperature for 1 h. Then the mixture was quenched with 5% HCl aqueous solution at 0 ℃ and extracted with AcOEt. Usual workup and purification by silica gel column chromatography (AcOEt/hexane 1/9) afforded **2** (20.0 mg, 88% isolated yield) with preference of (-)-(S)-enantiomer. The ee was determined to be 68% by chiral HPLC analysis (DAICEL CHIRALPAK AS, iPrOH/hexane 3/7, flow rate 0.5 ml/min, column temperature 35 ℃, retention time: (+)-**2** 43.0 min, (-)-**2** 56.2 min).

In summary, we have achieved the first asymmetric Cu-catalyzed conjugate addition of trialkylaluminium to cyclohexa-2,5-dienone **1** in the presence of 20 mol% of the chiral 2-aryloxazolines **3a-g** and 120 mol% of TBDMSOTf. Although the ee's are still unsatisfactory (up to 68% ee), the mild reaction conditions, ease of preparation and stability of the chiral ligands are all very encouraging. Further examination of new catalysts and mechanistic studies are underway in our laboratory to achieve a much higher ee.

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9. Toda, F.; Tanaka, K. *Tetrahedron Lett.* **1988**, *29*, 551-554: The absolute configuration of major product (-)-**2** was determined by a single X-ray crystallographic analysis of a 1:1 complex of (-)-*trans*-α,α'-(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) and (-)-**2**, which was isolated from the enantiomeric mixture of **2** by the chiral HPLC [(-)-(*S*)-**2** (88% ee): $[\alpha]_D^{24}$ -92.0 (*c* 0.565, $CHCl_3$), (+)-(*R*)-**2** (>99% ee): $[\alpha]_D^{26}$ +101.7 (*c* 0.530, $CHCl_3$)]. The details of the X-ray crystallographic analysis will be described in a full paper in near future.
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